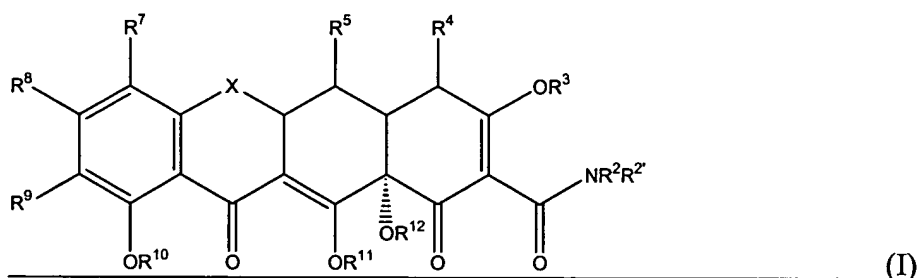


AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions of the claims and listing of the claims in the application:

1. **(Currently Amended)** A method for treating or preventing malaria in a subject, comprising administering to said subject an effective amount of a substituted tetracycline compound, of formula I:



wherein:

X is CR^{6'}R⁶;

R², R^{2'}, R^{4'}, and R^{4''} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R⁴ is NR^{4'}R^{4''}, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R³, R¹¹ and R¹² are each hydrogen, or a pro-drug moiety;

R¹⁰ is hydrogen, a prodrug moiety, or linked to R⁹ to form a ring;

R⁵ is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R⁶ and R^{6'} are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R⁷ is a malaria interacting moiety;

R⁹ is hydrogen;

R⁸ is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and pharmaceutically acceptable salts thereof, such that malaria is treated or prevented in said subject.

2. **(Cancelled)**

3. **(Currently Amended)** The method of claim 2 ~~1~~, wherein R^2 , $R^{2'}$, R^3 , R^8 , R^{10} , R^{11} , and R^{12} are hydrogen; R^4 is $NR^{4'}R^{4''}$; $R^{4'}$ and $R^{4''}$ are alkyl, and X is $CR^6R^{6'}$.

4. **(Currently Amended)** The method of claim 3, wherein R^5 , R^6 , and $R^{6'}$ are each hydrogen, ~~and R^7 is dimethylamino.~~

5. **(Currently Amended)** The method of claim 3, wherein R^5 is hydroxy or a prodrug moiety, R^6 is methyl, and $R^{6'}$ is hydrogen ~~and R^7 is hydrogen.~~

6.-25. **(Cancelled)**

26. **(Original)** The method of claim 3, wherein R^7 is a malaria interacting moiety.

27. **(Original)** The method of claim 26, wherein R^7 comprises 4 to 20 carbon, nitrogen, sulfur, or oxygen atoms.

28. **(Original)** The method of claim 26, wherein said malaria interacting moiety comprises an aryl group.

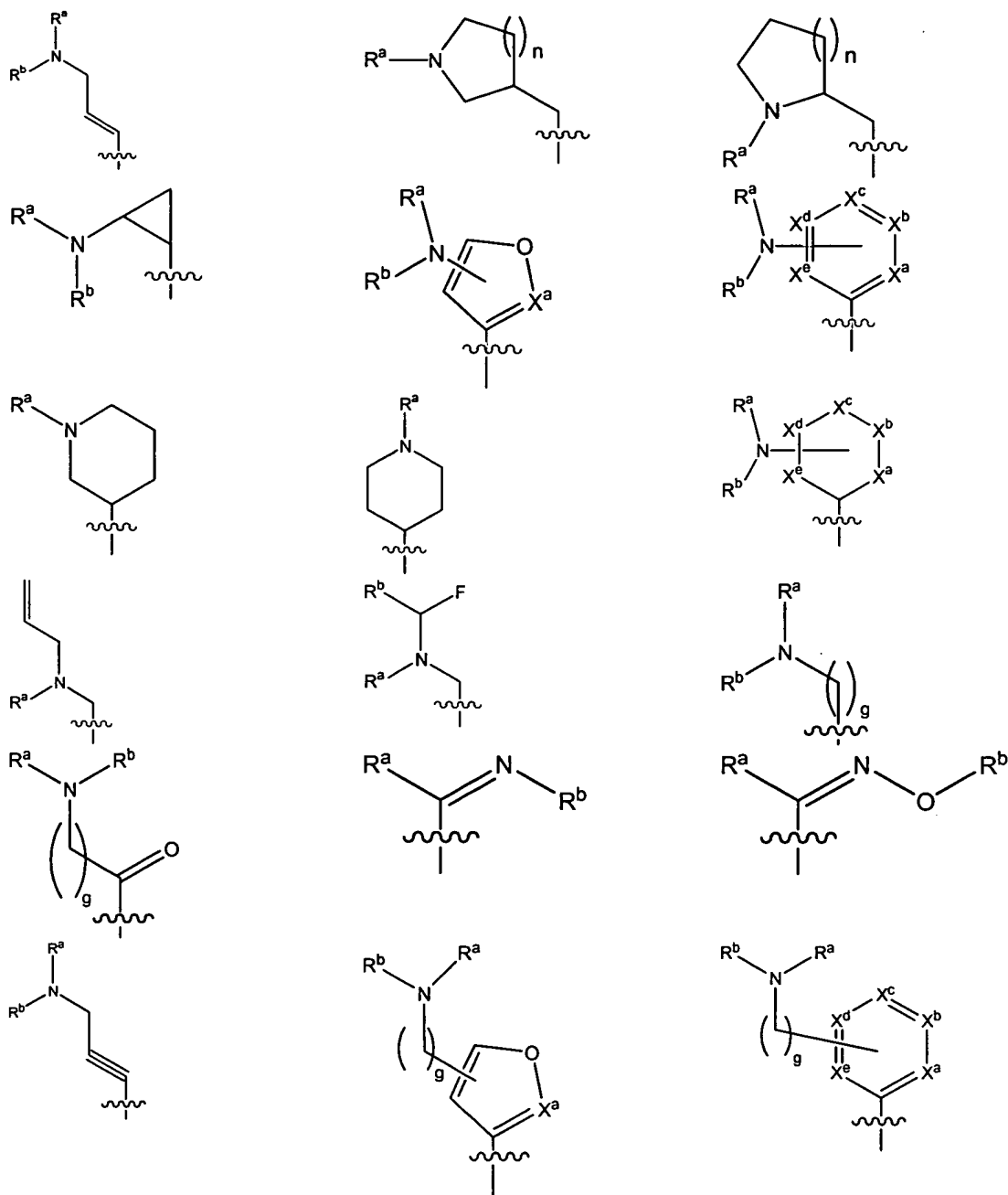
29. **(Original)** The method of claim 28, wherein said aryl group is substituted or unsubstituted phenyl.

30. **(Original)** The method of claim 29, wherein said phenyl group is substituted with halogen, alkoxy, amino, acyl, alkyl, nitro, formyl, amido, alkyl, alkenyl, alkynyl, or aryl.

31. **(Original)** The method of claim 30, wherein said alkoxy group is methoxy, ethoxy, propoxy, methylene dioxy, or ethylene dioxy.

32. **(Original)** The method of claim 30, where said alkyl group is substituted or substituted methyl, ethyl, propyl, butyl or pentyl.

33. **(Original)** The method of claim 32, wherein said alkyl group is substituted with an amino, carbocyclic or heterocyclic group.
34. **(Original)** The method of claim 30, wherein said acyl group is acetyl.
35. **(Original)** The method of claim 28, wherein said aryl group is substituted or unsubstituted heteroaryl.
36. **(Original)** The method of claim 35, wherein said heteroaryl is thienyl, imidazolyl, pyrrolyl, pyridinyl, furanyl, pyrimidinyl, or benzofuranyl.
37. **(Original)** The method of claim 26, wherein said malaria interacting moiety is substituted or unsubstituted alkynyl.
38. **(Original)** The method of claim 37, wherein said alkynyl is substituted with a substituted or unsubstituted aryl group.
39. **(Original)** The method of claim 26, wherein said malaria interacting moiety is alkyl or alkenyl.
40. **(Original)** The method of claim 26, wherein said malaria interacting moiety is C₁-C₁₅.
41. **(Original)** The method of claim 26, wherein said malaria interacting moiety is substituted carbonyl.
42. **(Original)** The method of claim 26, wherein said malaria interacting moiety comprises an ionizable nitrogen atom.
43. **(Original)** The method of claim 26, wherein said malaria interacting moiety is selected from the group consisting of:



wherein:

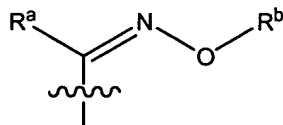
R^a and R^b are each independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, or heterocyclic;

g is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20;

n is 0, 1, 2, or 3; and

X^a , X^b , X^c , X^d , and X^e are each independently optionally substituted carbon, oxygen, nitrogen, or sulfur.

44. **(Original)** The method of claim 43, wherein said malaria interacting moiety is

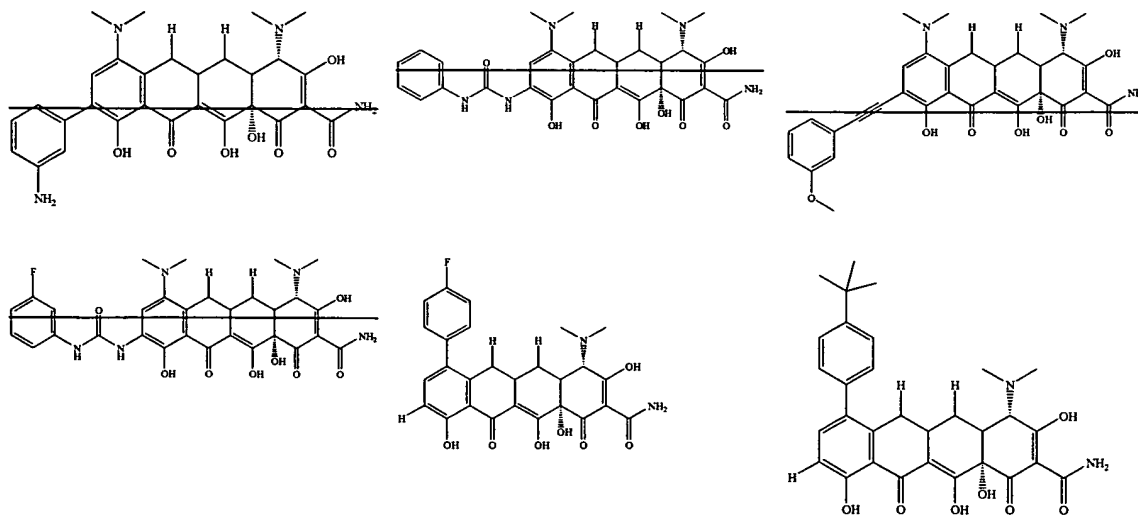


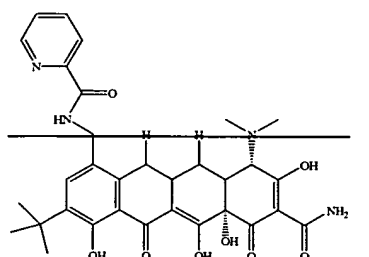
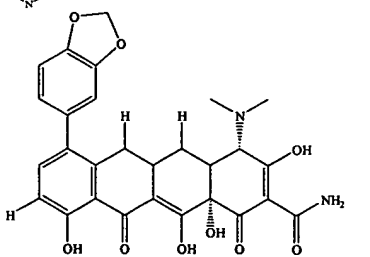
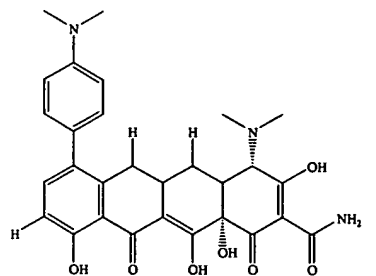
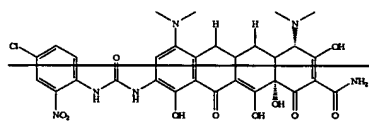
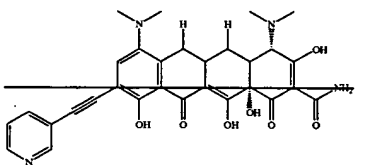
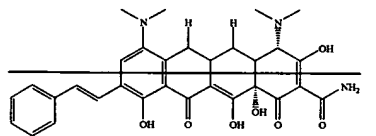
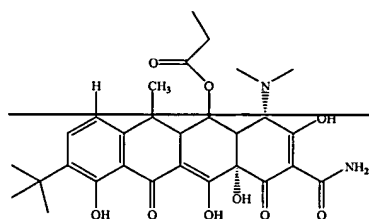
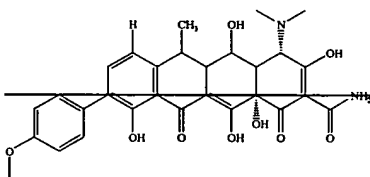
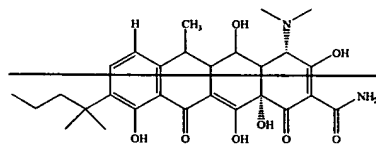
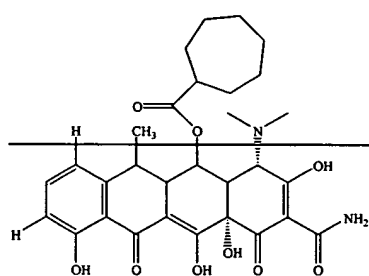
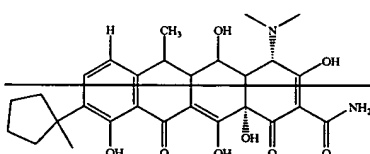
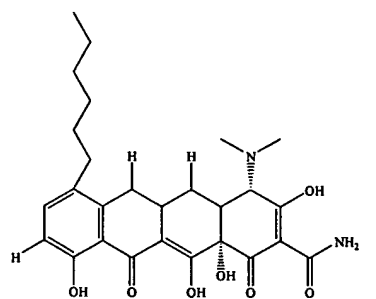
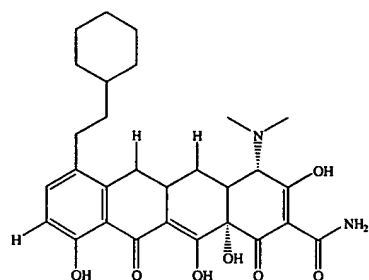
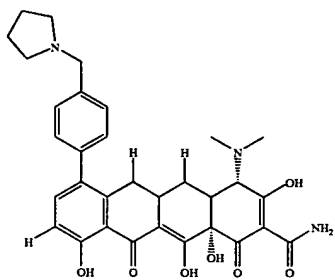
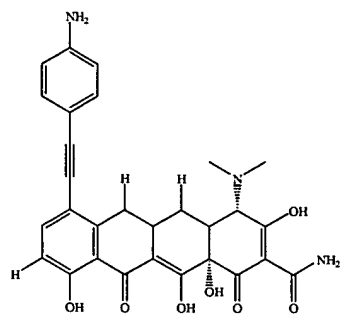
45. **(Original)** The method of claim 44, wherein R^a and R^b are each alkyl.

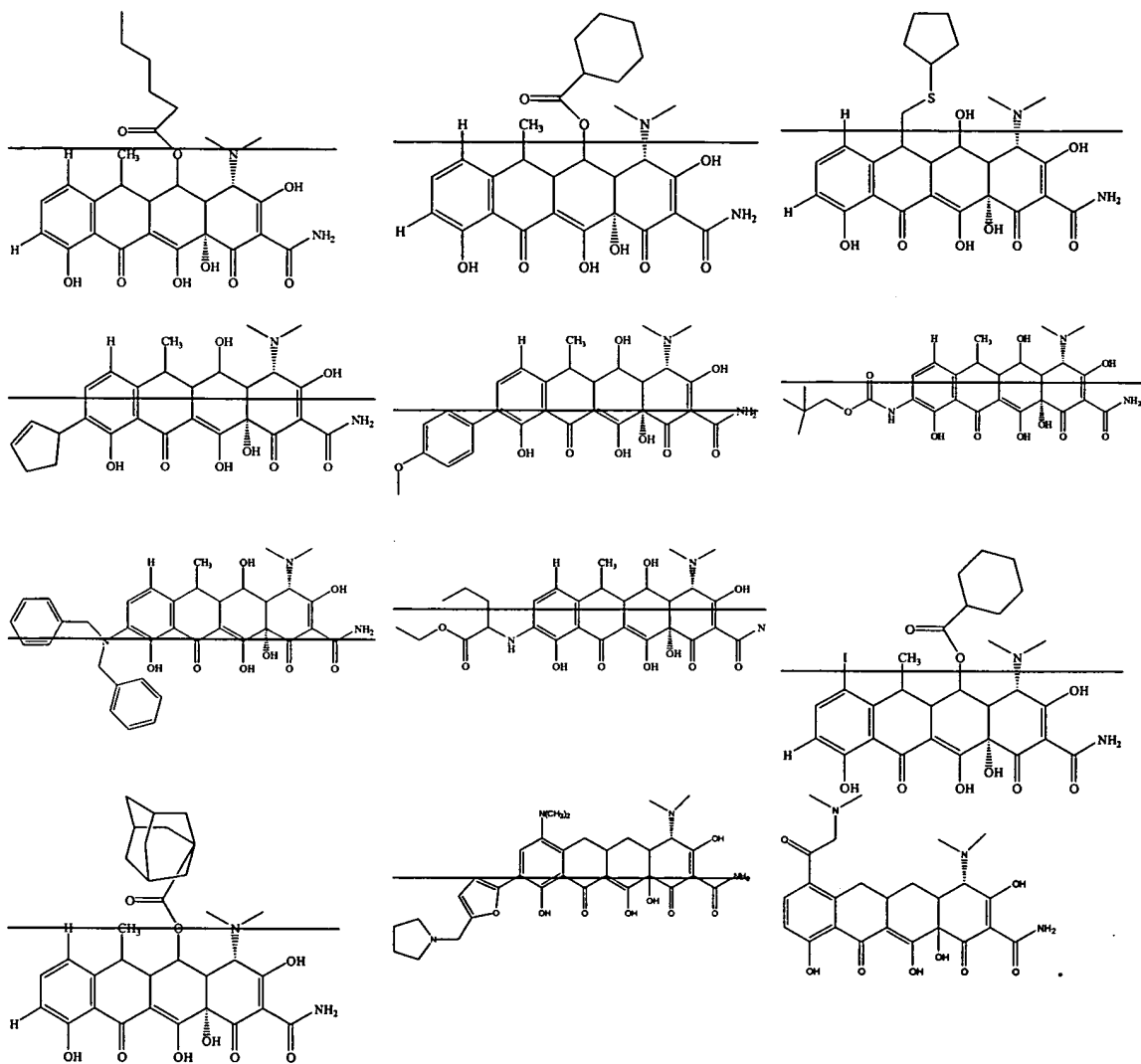
46. **(Cancelled)**

47. **(Cancelled)**

48. **(Currently Amended)** The method of claim 2 1, wherein said compound is selected from the group consisting of:

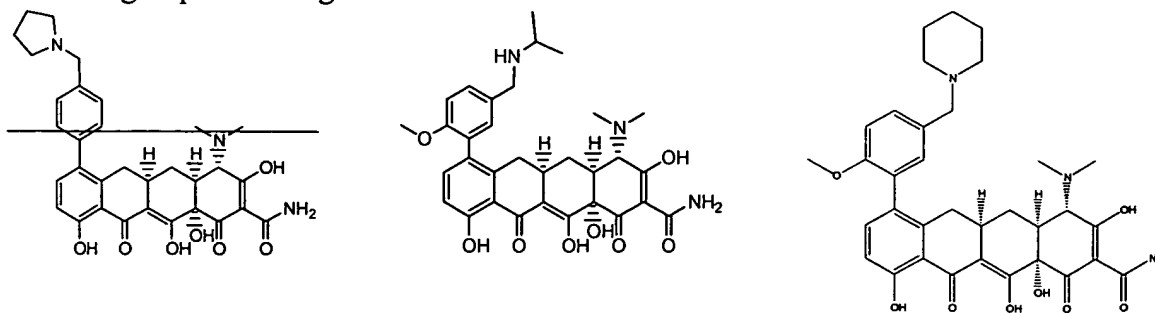


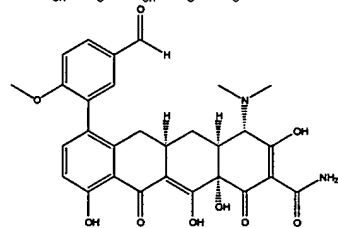
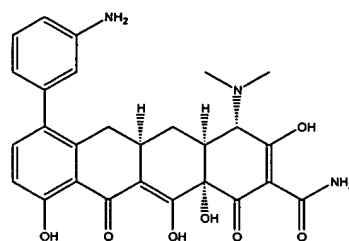
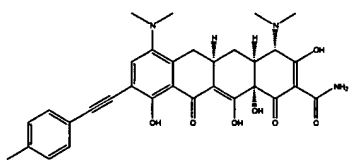
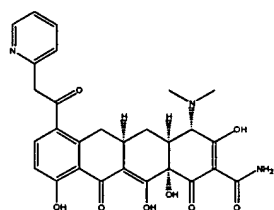
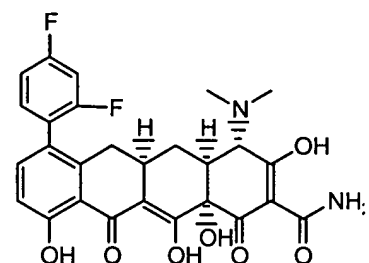
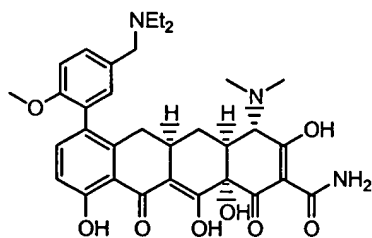
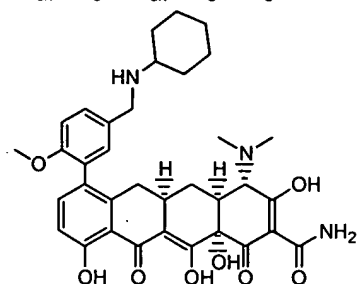
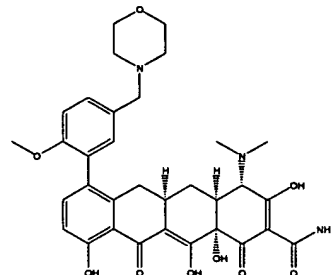
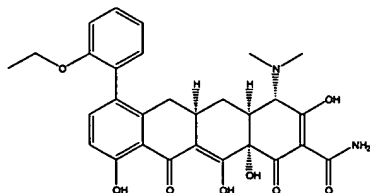
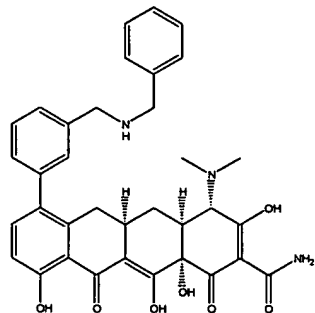
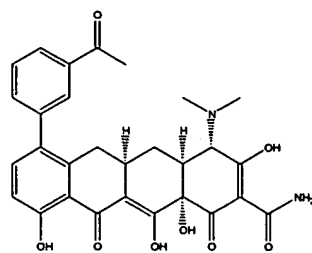
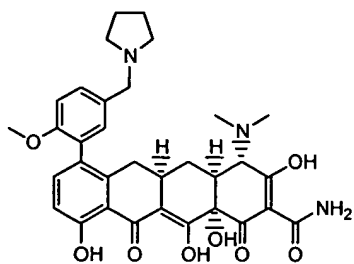
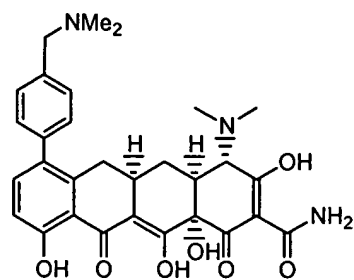


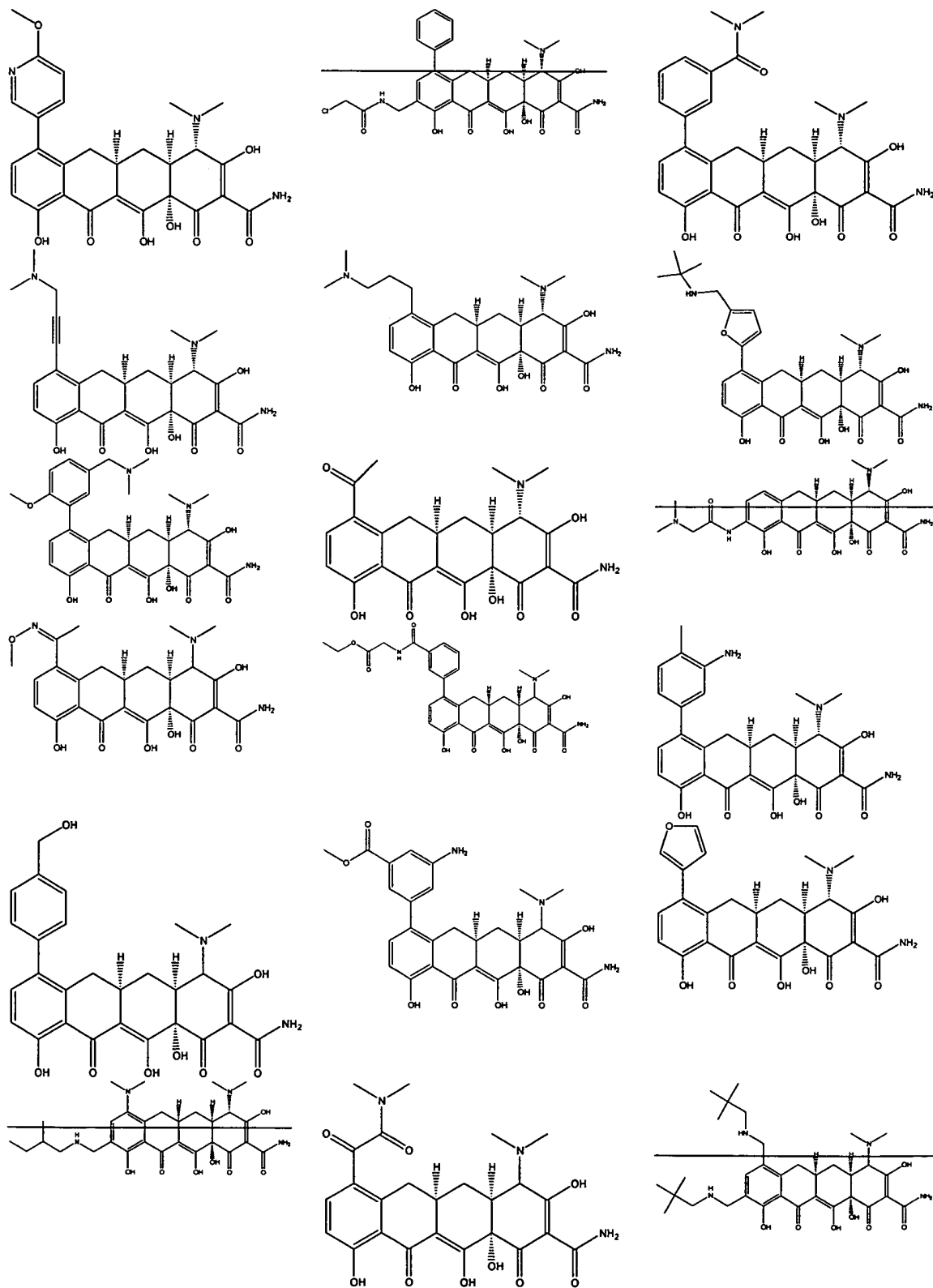


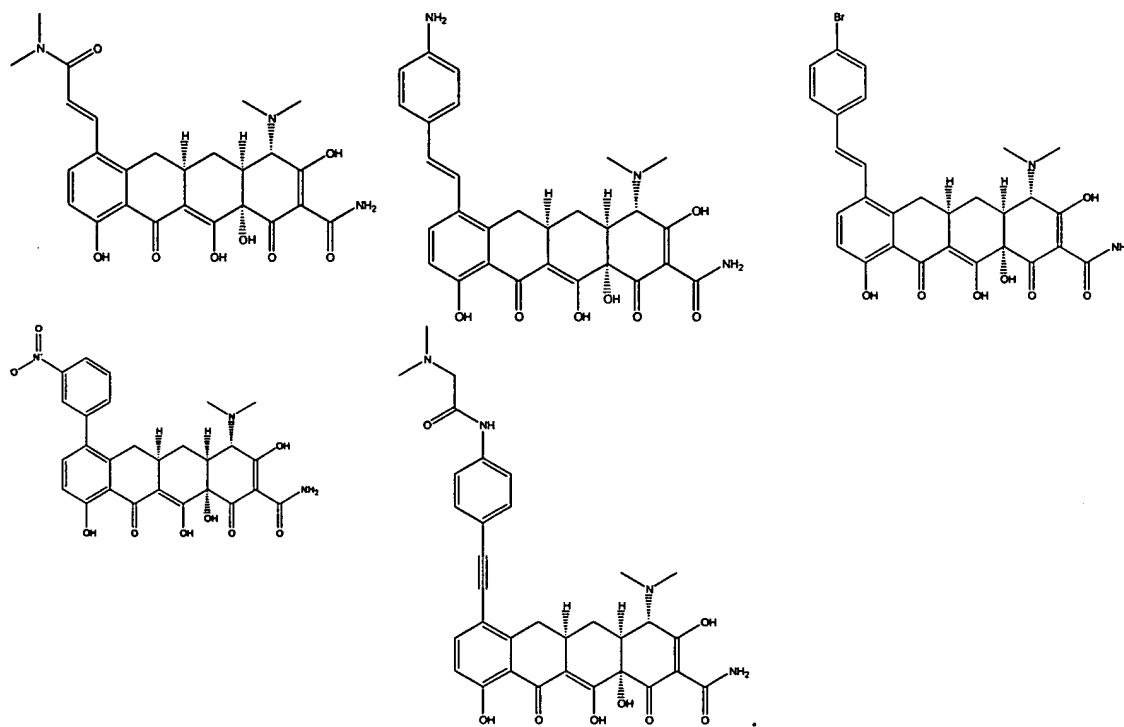
49. **(Currently Amended)**
 from the group consisting of:

The method of claim 2 1, wherein said compound is selected









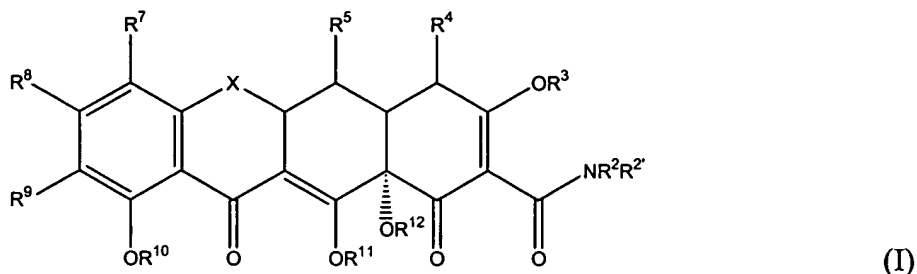
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56. **(Original)** The method of claim 1, wherein said substituted tetracycline compound has a cytotoxicity of 25 $\mu\text{g/ml}$ or greater.
57. **(Original)** The method of claim 1, wherein said substituted tetracycline compound has a MIC of 150 nM or less.
58. **(Original)** The method of claim 57, wherein said substituted tetracycline compound has a MIC of 50 nM or less.
59. **(Original)** The method of claim 58, wherein said substituted tetracycline compound has a MIC of 10 nM or less.
60. **(Original)** The method of claim 59, wherein said substituted tetracycline compound has an MIC or 5 nM or less.
61. **(Original)** The method of claim 1, wherein said malaria is caused by a plasmodium protozoan selected from the group consisting of: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*.
62. **(Original)** The method of claim 1, wherein said malaria is resistant to one or more anti-malarial compounds selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, proguanil, and 1,16-hexadecamethylenebis(N-methylpyrrolidinium) dibromide.
63. **(Original)** The method of claim 1, further comprising administering a supplementary compound.
64. **(Original)** The method of claim 63, wherein said supplementary compound treats a symptom selected from the group consisting of: headache, malaise, anemia, splenomegaly, and fever.

65. **(Original)** The method of claim 64, wherein said supplementary compound is an anti-malarial compound.

66. **(Original)** The method of claim 65, wherein said anti-malarial compound is selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide, and combinations thereof.

67. **(Currently Amended)** A method for increasing the antimalarial activity of an antimalarial compound, comprising administering said antimalarial compound in combination with an effective amount of a substituted tetracycline compound, such that the antimalarial activity of said antimalarial compound is increased, wherein said tetracycline compound is of formula I:



wherein:

X is CR^{6'}R⁶;

R², R^{2'}, R^{4'}, and R^{4''} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R⁴ is NR^{4'}R^{4''}, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R³, R¹¹ and R¹² are each hydrogen, or a pro-drug moiety;

R¹⁰ is hydrogen, a prodrug moiety, or linked to R⁹ to form a ring;

R⁵ is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 is ~~hydrogen, alkylamino, dialkylamino, or a malaria interacting moiety;~~

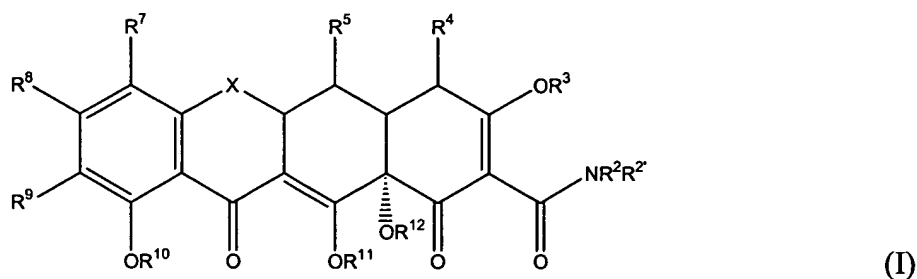
R^9 is ~~hydrogen, or a malaria interacting moiety;~~

R^8 is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

~~with the proviso that the compound of formula I is not oxytetracycline, demeclocycline, doxycycline, chlorotetracycline, minocycline, or tetracycline;~~ and pharmaceutically acceptable salts thereof.

68. **(Original)** The method of claim 67, wherein said anti-malarial compound is selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide, and combinations thereof.

69. **(Currently Amended)** A method for preventing malaria in a mammal, comprising administering to said mammal an effective amount of a substituted tetracycline compound, such that malaria is prevented in said mammal, wherein said tetracycline compound is of formula I:



wherein:

X is $CR^{6'}R^6$;

R^2 , $R^{2'}$, $R^{4'}$, and $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R^3 , R^{11} and R^{12} are each hydrogen, or a pro-drug moiety;

R^{10} is hydrogen, a prodrug moiety, or linked to R^9 to form a ring;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

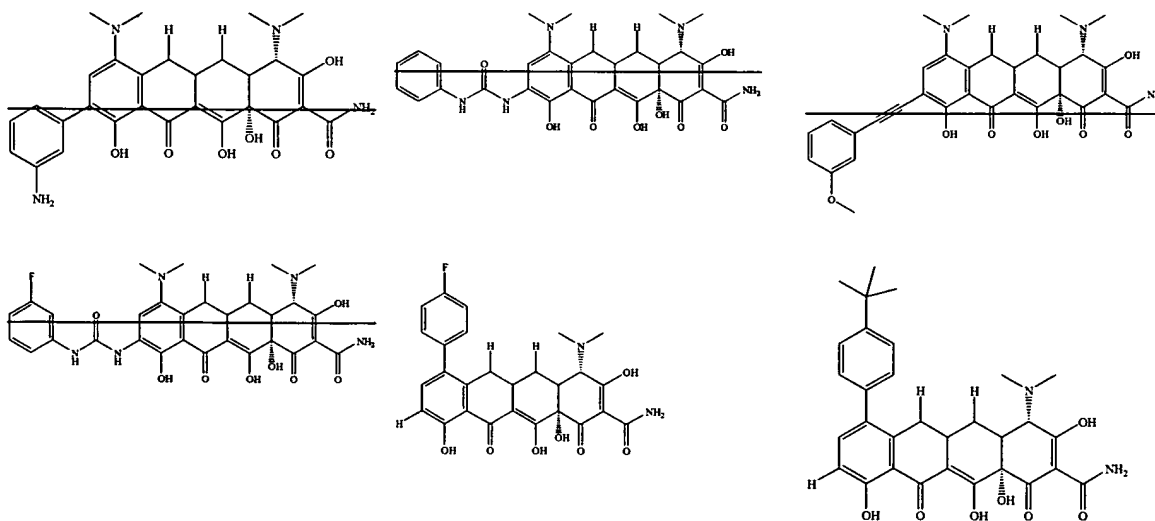
R^7 is ~~hydrogen, alkylamino, dialkylamino, or~~ a malaria interacting moiety;

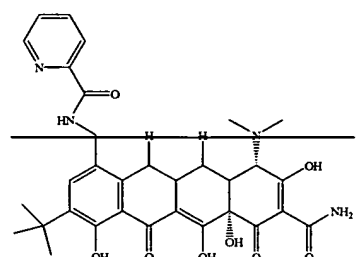
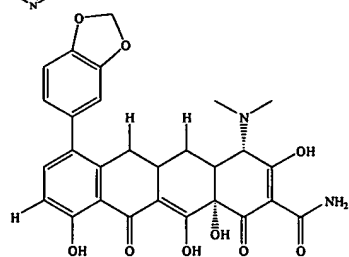
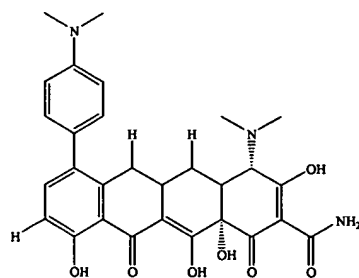
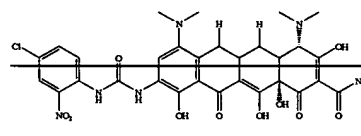
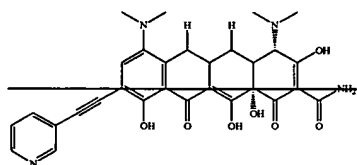
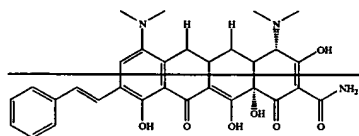
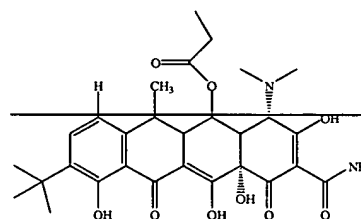
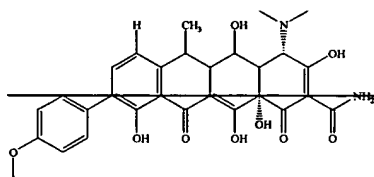
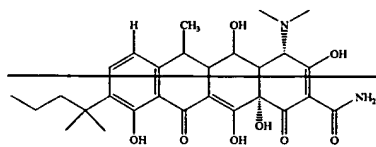
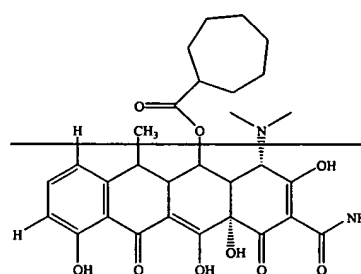
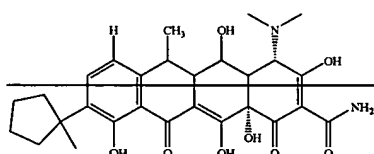
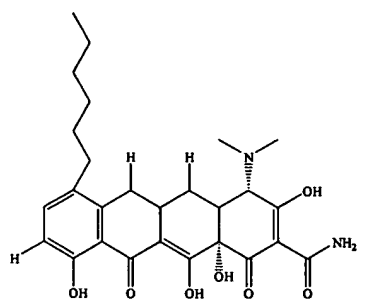
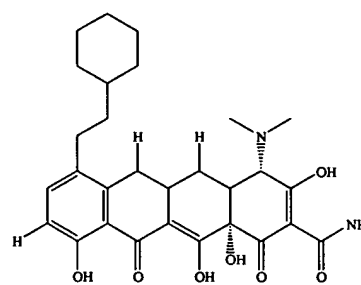
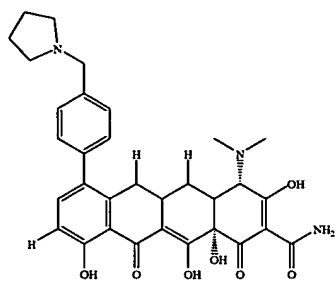
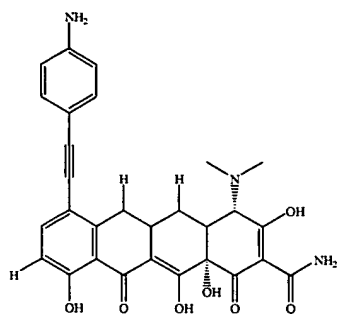
R^9 is ~~hydrogen, or a malaria interacting moiety;~~

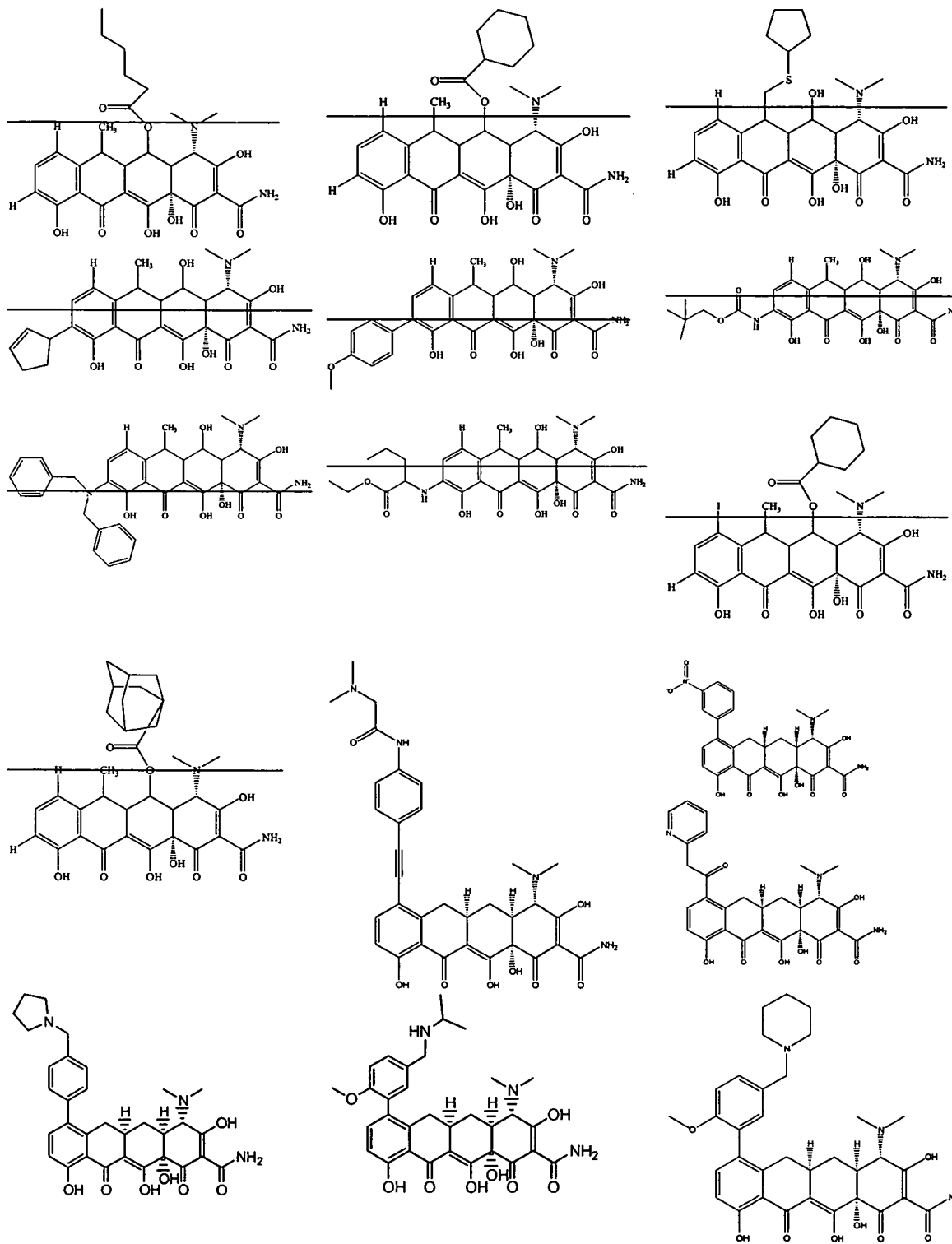
R^8 is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

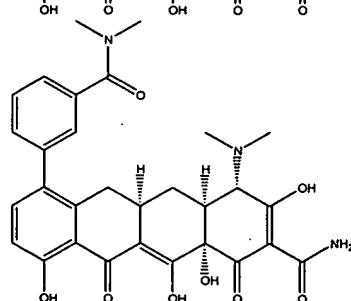
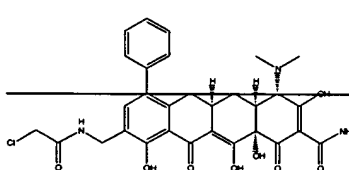
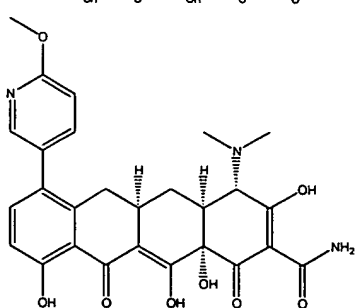
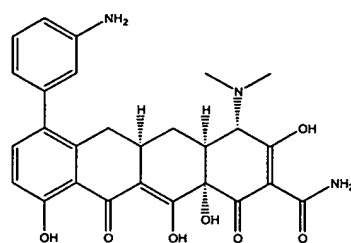
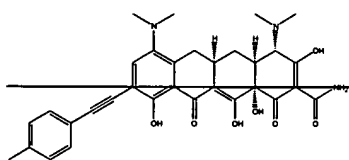
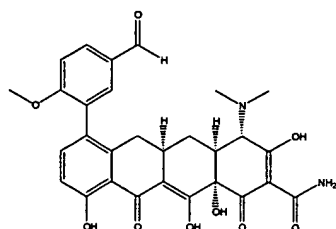
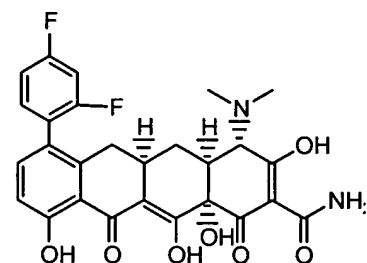
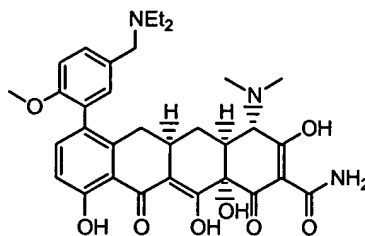
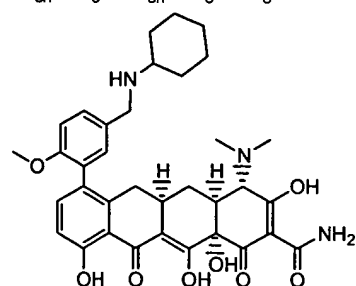
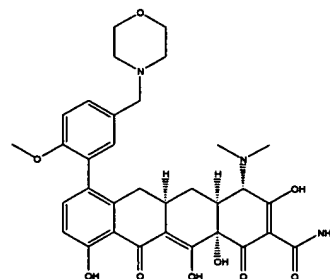
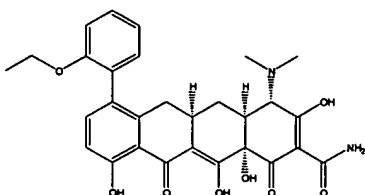
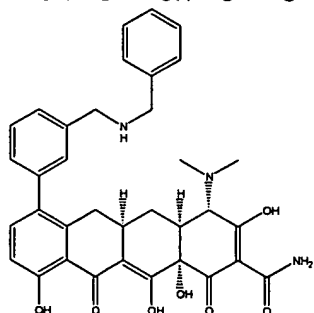
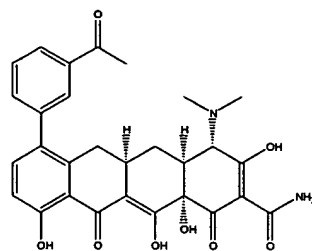
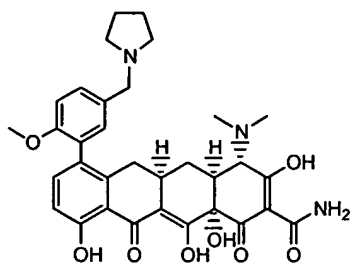
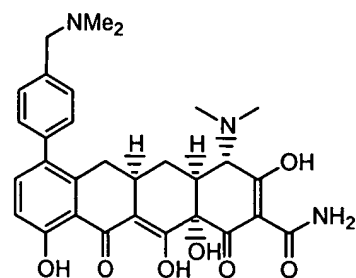
~~with the proviso that the compound of formula I is not oxytetracycline, demeclocycline, doxycycline, chlorotetracycline, minocycline, or tetracycline;~~ and pharmaceutically acceptable salts thereof.

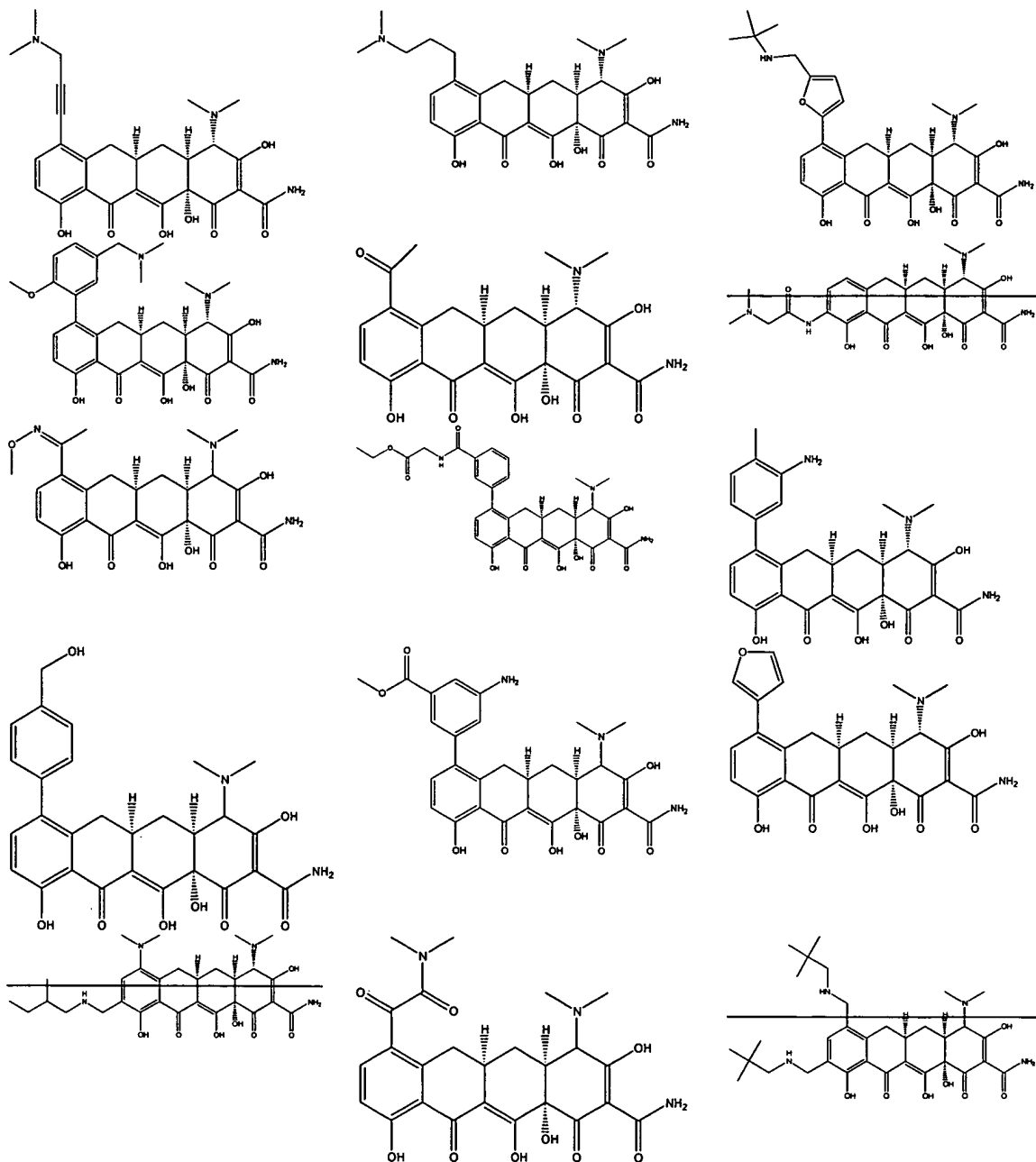
70. **(Currently Amended)** The method of claim 69, wherein said substituted tetracycline compound is selected from the group consisting of:

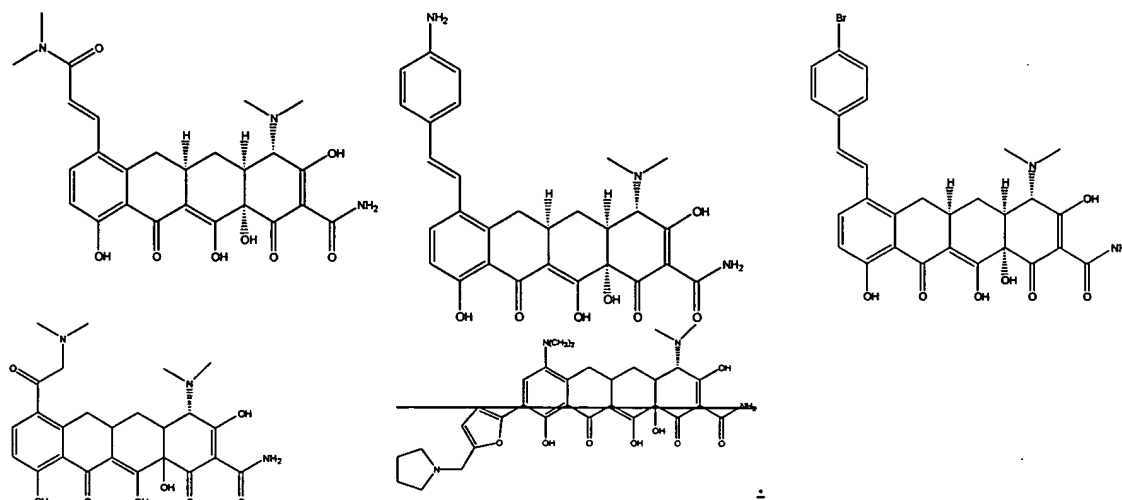












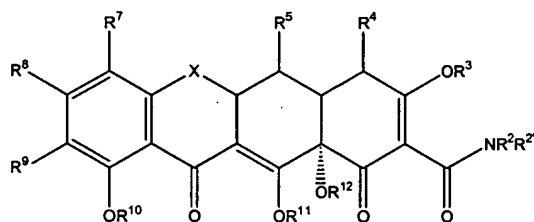
71. **(Original)** The method of claim 67 or 69, wherein said substituted tetracycline compound is a compound shown in Table 1 or Table 2.
72. **(Original)** The method of claim 67 or 69, wherein said substituted tetracycline compound is non-antibacterial.
73. **(Original)** The method of claim 67 or 69, wherein said substituted tetracycline compound is has anti-microbial gram positive activity.
74. **(Original)** The method of claim 73, wherein said anti-microbial gram positive activity is greater than about 0.05 $\mu\text{g/ml}$.
75. **(Original)** The method of claim 74, wherein said anti-microbial gram positive activity is greater than about 5 $\mu\text{g/ml}$.
76. **(Original)** The method of claim 75, wherein said substituted tetracycline compound has a cytotoxicity of 25 $\mu\text{g/ml}$ or greater.
77. **(Original)** The method of claim 67 or 69, wherein said substituted tetracycline compound has a MIC of 150 nM or less.

78. **(Original)** The method of claim 77, wherein said substituted tetracycline compound has a MIC of 50 nM or less.

79. **(Original)** The method of claim 78, wherein said substituted tetracycline compound has a MIC of 10 nM or less.

80. **(Original)** The method of claim 79, wherein said substituted tetracycline compound has an MIC of 5 nM or less.

81. **(Currently Amended)** A pharmaceutical composition comprising an effective amount of a substituted tetracycline compound to treat malaria in a mammal and a pharmaceutically acceptable carrier, wherein said tetracycline compound is of formula I:



wherein:

X is CR^{6'}R⁶;

R², R^{2'}, R^{4'}, and R^{4''} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R⁴ is NR^{4'}R^{4''}, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R³, R¹¹ and R¹² are each hydrogen, or a pro-drug moiety;

R¹⁰ is hydrogen, a prodrug moiety, or linked to R⁹ to form a ring;

R⁵ is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

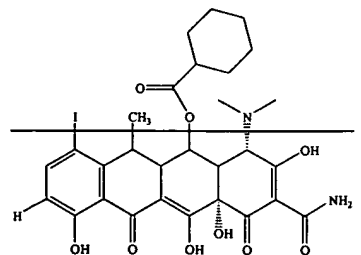
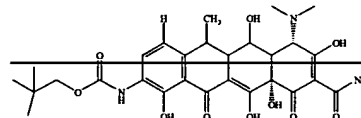
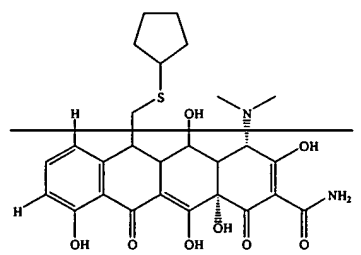
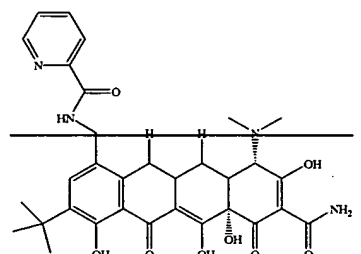
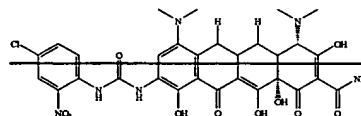
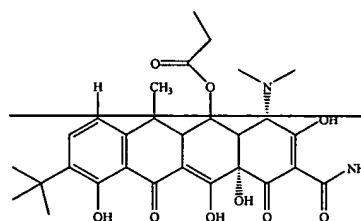
R⁶ and R^{6'} are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

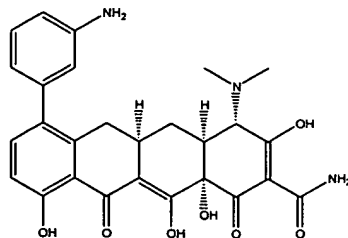
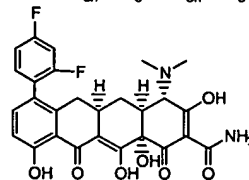
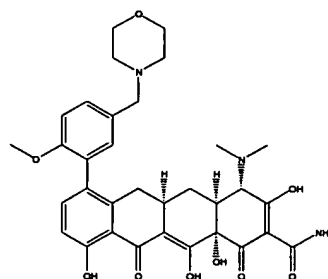
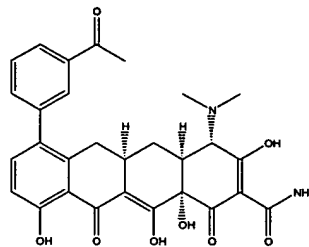
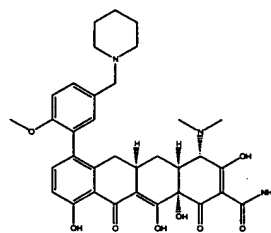
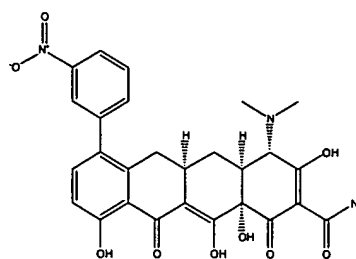
R⁷ is hydrogen, alkylamino, dialkylamino, or a malaria interacting moiety;

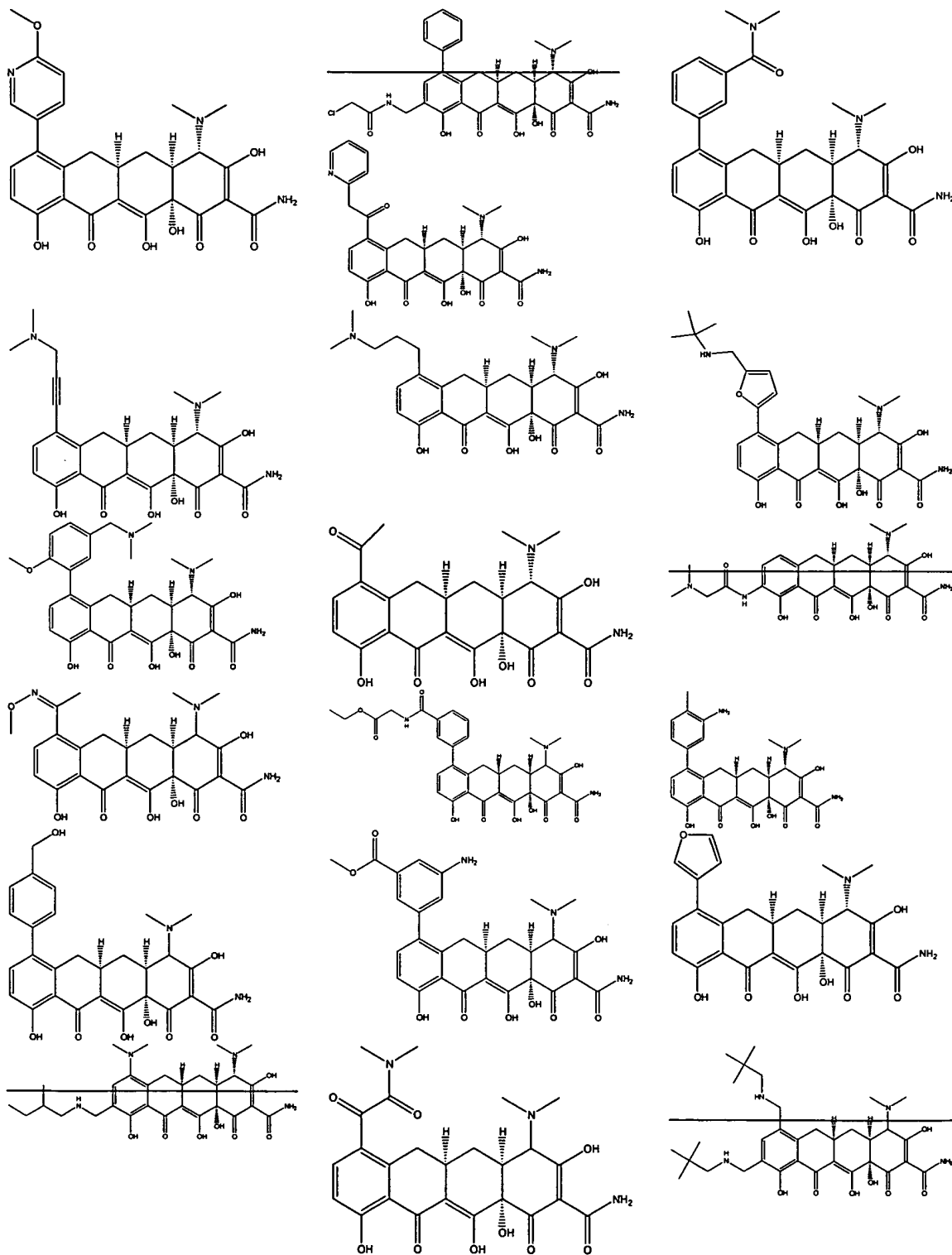
R⁹ is hydrogen, or a malaria interacting moiety;

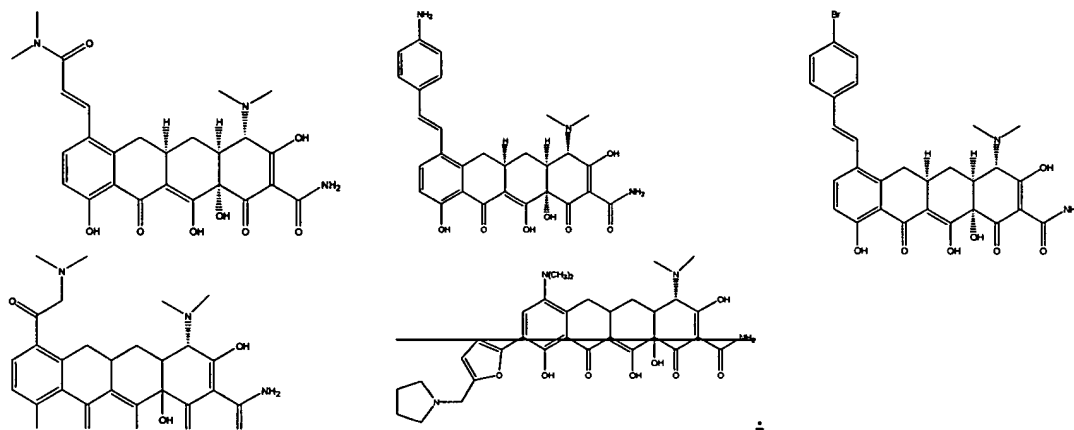
with the proviso that the compound of formula I is not oxytetracycline, demeclocycline, doxycycline, chlorotetracycline, minocycline, or tetracycline; and pharmaceutically acceptable salts thereof.

[illegible]









83. **(Original)** The pharmaceutical composition of claim 81, wherein said substituted tetracycline compound is a compound shown in Table 1 or Table 2.

84. **(Original)** The pharmaceutical composition of claim 81, further comprising a secondary agent.

85. **(Original)** The pharmaceutical composition of claim 84, wherein the secondary agent is selected from the group consisting of proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide and pyronaridine.

86. **(Cancelled)**

87. **(Previously Presented)** The method of claim 1, wherein the substituted tetracycline compound is

